IN THE CLAIMS

Please replace all prior versions, and listings, of claims in the application with the following list of claims. Additions are indicated by underlining and deletions are indicated by strikeouts and/or double bracketing.

1-44. (Cancelled)

45. (Currently Amended) In a method of producing a chip comprising a predetermined reaction site having a volume of less than 1 ml, the improvement comprising:

attaching a first component of the chip to a second component of the chip with or without auxiliary adhesive to produce a portion of the chip that defines the predetermined reaction site, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site; and

attaching a membrane substantially transparent to incident electromagnetic radiation in the infrared to ultraviolet range having a pore size less than 2.0 microns to the chip such that the membrane is in fluid communication with the predetermined reaction site.

46. (Cancelled)

47. (Original) The method of claim 45, wherein the improvement comprises sonic welding the first component to the second component.

48. (Original) The method of claim 45, wherein the improvement comprises heat pressing the first component to the second component

49. (Previously Presented) The method of claim 45, wherein the first component comprises at least one polymer selected from the group consisting of polycarbonate, polysulfone, polyethylene, and blends and copolymers thereof.

50. (Original) The method of claim 45, wherein the improvement comprises applying energy to melt at least a portion of the first component.

51. (Original) The method of claim 50, wherein the energy comprises ultrasound.

52. (Original) The method of claim 50, wherein the energy comprises heat energy.

53. (Original) The method of claim 45, wherein the improvement comprises attaching the first component to the second component to produce a liquid-tight junction therebetween.

54. (Previously Presented) The method of claim 45, wherein the chip is enclosed.

55-119. (Cancelled)

120. (New) An apparatus, comprising:

a substantially liquid-tight chip comprising a predetermined reaction site having a volume of less than about 2 ml, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

121. (New) The apparatus of claim 120, wherein the chip comprises structural components interconnected without auxiliary adhesive at locations defining boundaries of the predetermined reaction site.

122. (New) The apparatus of claim 120, wherein the predetermined reaction site, during use of the chip, is not in fluid communication with an adhesive.

123. (New) The apparatus of claim 120, further comprising a membrane defining at least a portion of the predetermined reaction site.

124. (New) The apparatus of claim 123, wherein the membrane is an oxygen-permeable membrane.

125. (New) The apparatus of claim 123, wherein the membrane is a CO_2-permeable membrane.

126. (New) The apparatus of claim 123, wherein the membrane is porous.

127. (New) The apparatus of claim 123, wherein the membrane is substantially transparent.

128. (New) The apparatus of claim 123, wherein the membrane comprises at least one of polycarbonate, cellulose, nitrocellulose, glass, fiberglass, or polycarbonate, regenerated cellulose, or polyethylene.

129. (New) The apparatus of claim 120, further comprising a temperature sensor in sensing communication with the predetermined reaction site.

130. (New) The apparatus of claim 120, further comprising a pH sensor in sensing communication with the predetermined reaction site.

131. (New) The apparatus of claim 120, further comprising a pressure sensor in sensing communication with the predetermined reaction site.

132. (New) An apparatus, comprising:

a predetermined reaction site having a volume of less than about 1 ml; and

a membrane substantially transparent to incident electromagnetic radiation in the infrared to ultraviolet range having a pore size less than 2.0 microns in fluid communication with the predetermined reaction site.

133. (New) The apparatus of claim 132, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

134. (New) The apparatus of claim 132, further comprising a membrane defining at least a portion of the predetermined reaction site.

135. (New) The apparatus of claim 134, wherein the membrane is an oxygen-permeable membrane.

136. (New) The apparatus of claim 134, wherein the membrane is a CO_2-permeable membrane.

137. (New) The apparatus of claim 134, wherein the membrane is porous.

138. (New) The apparatus of claim 134, wherein the membrane is substantially transparent.

139. (New) The apparatus of claim 134, wherein the membrane comprises at least one of polycarbonate, cellulose, nitrocellulose, glass, fiberglass, or polycarbonate, regenerated cellulose, or polyethylene.

140. (New) The apparatus of claim 132, further comprising a temperature sensor in sensing communication with the predetermined reaction site.

141. (New) The apparatus of claim 132, further comprising a pH sensor in sensing communication with the predetermined reaction site.

142. (New) The apparatus of claim 132, further comprising a pressure sensor in sensing communication with the predetermined reaction site.

143. (New) An apparatus, comprising:

a predetermined reaction site having a volume of less than about 2 ml; and

a membrane substantially transparent to incident electromagnetic radiation in the infrared to ultraviolet range having a pore size less than 2.0 microns in fluid communication with the predetermined reaction site.

144. (New) The apparatus of claim 143, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

145. (New) An apparatus, comprising:

a chip comprising a predetermined reaction site having an inlet, an outlet, and a volume of less than about 2 ml, the predetermined reaction site constructed and arranged to maintain at least one living cell at the predetermined reaction site,

wherein the chip is constructed and arranged to stably connect in a predetermined, aligned relationship to other, similar chips.

146. (New) An apparatus, comprising:

a chip comprising a predetermined reaction site having an inlet, an outlet, and a volume of less than about 2 ml, wherein the chip is constructed and arranged to be stably connectable to a microplate.

147. (New) An apparatus, comprising:

a chip comprising a predetermined reaction site having an inlet, an outlet, and a volume of less than about 2 ml, wherein the chip is constructed and arranged to be fluid communicable with an apparatus constructed and arranged to address a well of a microplate.

148. (New) An apparatus, comprising:

a chip comprising a predetermined reaction site having an inlet, an outlet, and a

volume of less than about 2 ml, wherein each predetermined reaction site overlaps at least one well of a microplate.

149. (New) An apparatus, comprising:

a chip produced by a process including the step of fastening two components to produce a portion of the chip defining a predetermined reaction site having a volume of less than about 2 ml, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

150. (New) A system, comprising:

an apparatus constructed and arranged to secure a biological substrate, wherein the apparatus is able, independently, to rotate the biological substrate about an axis, and translationally move the biological substrate in at least one of a direction substantially perpendicular to the axis and a direction substantially parallel to the axis.

151. (New) A method for screening a plurality of test compounds, the method comprising:

providing substrate having a surface into which is fabricated a plurality of cell culture chambers having a volume less than about 1000 μl and containing cells, each of the cell culture chambers being fluidly connected to at least a first and a second microchannel fabricated into the surface of the substrate;

culture chambers being fluidly connected to at least a first and a second microchannel fabricated into the surface of the substrate;

introducing each of the plurality of test compounds into at least one of the plurality of cell culture chambers; and

monitoring the effect of each of the plurality of test compounds on a biological response of the cells.

152. (New) A microfermentor device comprising:

a polymeric substrate having at least one surface;

a plurality of reaction chambers, formed within the polymeric substrate, constructed to operate in parallel, each reaction chamber comprising a cell growth chamber having a volume of less than about 1000 µl fabricated into the surface of the substrate, the cell growth chamber being constructed and arranged to culture cells for at least a period of time sufficient to generate a product resulting from interaction of the cells with oxygen and/or nutrients and/or other compounds, each reaction chamber further comprising an inlet port for the aseptic introduction of compounds, an outlet port for withdrawing material from the reaction chamber, and a gas permeable membrane that is water vapor impermeable, positioned adjacent the cell growth chamber;

a gas headspace, associated with the cell growth chamber, comprising a gas inlet port and a gas outlet port; and

at least a first channel fabricated into the surface of the substrate and fluidly connected to the inlet port of the cell growth chamber, wherein the first channel is fluidly connected to a mixing chamber.

153. (New) A method for screening a plurality of test compounds, the method comprising:

providing a polymeric substrate having a surface into which is fabricated a plurality of reaction chambers constructed to operate in parallel, each reaction chamber comprising a cell growth chamber having a volume less than about 1000 µl and containing cells, each of the cell growth chambers being fluidly connected to at least a first and a second microchannel fabricated into the surface of the substrate, the cell growth chambers further comprising a gas permeable membrane that is water vapor impermeable, positioned adjacent the cell growth chamber, the polymeric substrate further comprising a gas headspace, associated with the cell growth chamber, comprising a gas inlet port and a gas outlet port;

introducing each of the plurality of test compounds into at least one of the plurality of cell growth chambers; and

monitoring the effect of each of the plurality of test compounds on a biological response of the cells using an optical sensor in optical communication with the cell growth chamber.

154. (New) A cellular microfermentor method comprising:

providing a polymeric substrate comprising a plurality of reaction chambers, each reaction chamber comprising a cell growth chamber having a volume of less than about 1000 μl, each reaction chamber further comprising an inlet port for the aseptic introduction of compounds, an outlet port for withdrawing a product from the reaction chamber, and a gas headspace comprising a gas inlet port and a gas outlet port, the polymeric substrate further comprising at least a first and a second channel fabricated into the surface of the substrate and fluidly connected to the cell growth chamber, and a gas permeable membrane that is water vapor impermeable, positioned adjacent the cell growth chamber;

operating at least some of the plurality of the reaction chambers in parallel, involving, for each reaction chamber, introducing a gas into the gas headspace via the gas inlet port and allowing oxygen permeation through the membrane to the cell growth chamber to facilitate culturing of the cells, and culturing cells for at least a period of time sufficient to generate a protein product resulting from interaction of the cells with oxygen and/or nutrients and/or other compounds; and

recovering, from a reaction involving the cells in the cell growth chamber, the protein product produced by the cells.

155. (New) A method, comprising:

providing a chip comprising a predetermined reaction site having an inlet, an outlet, and a volume of less than about 1 ml, the predetermined reaction site constructed and arranged to maintain at least one living cell at the site; and

optically addressing the predetermined reaction site.

156. (New) A method, comprising:

providing a predetermined reaction site having a volume of less than about 1 ml, the predetermined reaction site constructed and arranged to maintain at least one living cell at the site;

providing material in the predetermined reaction site, the material having a smallest dimension;

directing electromagnetic radiation having an average beam diameter less than the smallest dimension of the material;

allowing the electromagnetic radiation to interact with the material to produce altered radiation; and

determining the altered radiation.

157. (New) An apparatus, comprising:

a chip comprising a plurality of predetermined reaction sites each having a volume of less than about 1 ml; and

a sensor able to determine an environmental factor associated with at least one of the predetermined reaction sites, the factor being at least one of CO_2 concentration, glucose concentration, glutamine concentration, pyruvate concentration, apatite concentration, serum concentration, a concentration of a vitamin, a concentration of an amino acid, and a concentration of a hormone.

158. (New) An apparatus, comprising:

a device comprising a predetermined reaction site having a volume of less than about 1 ml; and

a sensor integrally connected to the device, the sensor comprising a dye, a fluorescent molecule, or a chromogenic molecule, wherein the sensor is able to determine an environmental factor associated with the predetermined reaction site, the environmental factor being at least one of pH, a concentration of a dissolved gas, molarity, osmolarity, glucose concentration, glutamine concentration, pyruvate concentration, apatite concentration, color, turbidity, a concentration of an amino acid, and a concentration of an ion.

159. (New) An apparatus, comprising:

a device comprising a predetermined reaction site having a volume of less than about 1 ml;

a first sensor integrally connected to the device, the first sensor able to determine at least one of temperature and pressure; and

a second sensor integrally connected to the device, the second sensor comprising a dye, a fluorescent molecule, or a chromogenic molecule, wherein the second sensor is able to determine a second environmental factor, the second environmental factor being at least one of pH, a concentration of a dissolved gas, molarity, osmolarity, glucose concentration, glutamine concentration, pyruvate concentration, apatite concentration, color, turbidity, a concentration of an amino acid, and a concentration of an ion.

160. (New) An apparatus, comprising:

a chip comprising a predetermined reaction site having an inlet, an outlet, and a volume of less than about 1 ml, the predetermined reaction site constructed and arranged to maintain at least one living cell at the predetermined reaction site,

wherein the chip is constructed and arranged to stably connect in a predetermined, aligned relationship to other, similar chips.

161. (New) An apparatus, comprising:

a chip comprising a predetermined reaction site having an inlet, an outlet, and a volume of less than about 1 ml, wherein the chip is constructed and arranged to be stably connectable to a microplate.

162. (New) An apparatus, comprising:

a chip comprising a predetermined reaction site having an inlet, an outlet, and a volume of less than about 1 ml, wherein the chip is constructed and arranged to be fluid communicable with an apparatus constructed and arranged to address a well of a microplate.

163. (New) An apparatus, comprising:

a chip comprising a predetermined reaction site having an inlet, an outlet, and a volume of less than about 1 ml, wherein each predetermined reaction site overlaps at least one well of a microplate.

164. (New) An apparatus, comprising:

a substantially liquid-tight chip comprising a predetermined reaction site having a volume of less than about 1 ml, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

165. (New) An apparatus, comprising:

a chip produced by a process including the step of fastening two components to produce a portion of the chip defining a predetermined reaction site having a volume of less than about 1 ml, wherein the predetermined reaction site is constructed and arranged to maintain at least one living cell at the predetermined reaction site.

166. (New) An apparatus, comprising:

a predetermined reaction site having a volume of less than about 1 ml; and

a membrane substantially transparent to incident electromagnetic radiation in the infrared to ultraviolet range having a pore size less than 2.0 microns in fluid communication with the predetermined reaction site.